Section of Pathology.

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The Part played by Injury and Repair in the Development of Cancer, with some Remarks on the Growth of Experimental Cancers.

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CAN we demonstrate experimentally the reason for the very localized starting point of a tumour, although a great number of epithelial cells had been in contact during days and weeks with the cancer-producing agent? (tar in the case of the experimental tar cancer).

Mice were tarred in the usual way till some of the animals showed early papillomata, which, when seen under the microscope, proved to be definitely localized epithelial hypertrophies. If tarring is continued at this stage of the experiment the skin of the mice tends to form numerous tumours in a very short time. On the other hand, if tarring is discontinued, only a very small number of tumours will appear. At this stage of the experiment we therefore stopped tarring. A few days afterwards we made incisions in the skin, taking care to make these incisions at places where no papillomata had appeared. These wounds very soon assume an oval shape and heal in the normal time. At first there is formed a layer of fibrin and dead cells, and under this material we very soon found the first indications of healing in the shape of new epithelial cells. In the majority of cases we found that new tumour-processes had formed in the healed or partly healed wounds. In some cases there were only two or three tumours in one scar, in others there were many more. I never observed that the whole scar was involved in the tumour process. Sometimes the tumour growths were so numerous that the scar could be localized with the greatest ease. I have just mentioned that the tumours appeared in some cases after the scar had healed and that the new epithelial cells—that is to say, cells never themselves in contact with the tar—produced in the course of these experiments primary growths. We know that there is a relation between tar and tumour formation; we now learn from these experiments that the liability to tumour formation can be transferred to daughter and grand-daughter cells without the cells showing any biological change microscopically. These tumours, which we produced just at the place where we wanted to see them, were very malignant and sometimes the whole scar and the surrounding tissue were very soon replaced by a typical cancer growth. We have thus an opportunity of obtaining a clearer insight into the local origin of tumours in a skin area over which all the cells have been in contact with the cancer-producing material. The animals every now and then receive minute wounds. These wounds may be so small that they escape attention. They heal as a rule very quickly and we may suppose that some of them will produce a tumour in the same way as was shown in our experiments. In a very short time these tumours may become larger than the little (often almost invisible) scars from which they originated. These experiments may have a general significance as regards the local origin of a tumour.

Some other experiments throw light on the much discussed question of the manner of extension of a tumour. When we study the earliest beginning of a tumour there is seen to be a local hypertrophic growth. Somewhat later the

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surrounding cells hypertrophy as well. This process is extended until at length there is present on the skin a hypertrophic proliferation, generally in the form of a papilloma. The way in which such a papilloma grows seems to indicate an influence of the central parts of the papilloma on the surrounding cells of the living organism, with the result that these also hypertrophy. At a later stage the central parts of the papilloma become transformed into cancer cells and we have noticed that the cancer cells influence the surrounding hypertrophied cells exactly in the same way as the hypertrophied cells have previously influenced the surrounding normal cells.

These observations on the growth of young tumours, as was demonstrated at the Cancer Congress held at Strasbourg in 1924, confirm the original view maintained by Virchow. It is of great importance to show in another way the influence of tumour cells upon the surrounding living cells of the organism.

At the beginning of this paper I demonstrated that under certain circumstances young (regenerating) epithelial cells are very susceptible to tumour formation. On the strength of that observation I carried out the following experiment on the mice:—

Tar was applied to the epilated skin until a few small papillomata appeared; we then stopped applying the tar. A few days later we made two small scarifications, one which was in contact with the tumour, the other at some distance, for the purpose of control. We marked the position of these wounds by rubbing in Chinese ink and after two or three days the wounds had become healed. Only a small black line under the newly-formed epithelium showed us the place at which the fine, small scalpel had cut through the upper part of the skin. The minute healing wound which either touched the tumour, or very nearly did so, showed some interesting changes. The whole mass of new epithelial cells in this wound has become transformed into hypertrophic growth. We have never seen such extensive changes in scars not in contact with a tumour.

There must be an influence exercised by the tumour cells on the cells of the scar. As these cells are very liable to become neoplastic, this influence may be clearly demonstrated. Just as we have seen in the instance of papilloma, the surrounding cells are predisposed to hypertrophic—and afterwards to real—tumour growth.

Summary.

(1) Injury may exercise a direct influence on tumour genesis in an extensive area of epithelial cells that are susceptible to tumour formation.

(2) The results of former experiments have made it probable that in the earliest stages of tumour formation the peripheral cells may exercise an influence on the cells in the immediate neighbourhood. When we effect a contact between the youngest tumour cells and cells which we know are very susceptible to develop a tumour, we can then clearly see the direct influence of the tumour cells on the other cells of the organism.

It will be the purpose of further cancer study to obtain a better insight into these intercellular activities.